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Cognitive reserve and neuropsychiatric disorders

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Cognitive reserve is used to explain individual differences in the use of active processes to preserve cognitive function in the presence of brain pathology. Cognitive reserve is difficult to quantify experimentally and studies rely largely on the use of proxy measures such as premorbid IQ, education and occupation. Nevertheless, powerful longitudinal study designs suggest that premorbid IQ modifies the neurodevelopmental process in schizophrenia and modulates the impact of neurodegeneration in dementia. Evidence from intelligence research suggests that dysfunction of a fronto-parietal network has explanatory power for the effect of cognitive reserve in both disorders.

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Introduction

The term 'reserve' refers to an unused capacity that can be called upon in times of need and is a concept that has been adopted to explain individual differences in the behavioural response to equivalent brain abnormalities [1]. 'Cognitive reserve' is used to explain individual differences in the recruitment of active neural processes to preserve cognition in the face of brain dysfunction. This was initially distinguished from 'brain reserve' which refers to individual differences in brain structure, such as brain size, dendritic branching or synapse count, that can affect the threshold for the clinical expression of brain abnormalities [2]. Recent evidence from the study of neural plasticity suggests that this distinction is less clear-cut. Active engagement of cognitive processes has been shown to modify synaptic structure and function beyond the age when the brain is fully developed [3,4]. Brain reserve is therefore not fixed but can accrue with experience thus providing the neural substrate for the employment or even improvement of cognitive reserve throughout life. Stern [2] introduced the term 'neural reserve' to refer to the dynamic process by which neural networks mediating cognitive function can be shaped by individual differences not only in genetic endowment but also in life experiences. He suggested that people with high neural reserve may be more efficient in the use of existing cognitive networks to compensate for the impact of neuropathology. A related concept is that of 'brain maintenance' proposed by Nyberg and colleagues [5]. This suggests that there are individual differences in the ability to stave off brain changes, the distinction here being one of resilience rather than compensation. Another mechanism that may contribute to cognitive reserve, also proposed by Stern [2], is 'neural compensation', which is the ability to activate alternative neural processes in order to overcome the impact of neuropathology.

The concept of cognitive reserve, as an active brain mechanism to preserve cognitive function, emerged from the study of dementia but has subsequently been invoked as an explanation of the variability in outcome for other brain disorders such as multiple sclerosis [6] and acquired brain damage [7–9]. Cognitive reserve also has explanatory power for understanding prognosis in disorders thought to have their roots in abnormal or derailed brain development, such as schizophrenia and affective disorders [10]. In the following sections we focus on recent research as to how cognitive reserve influences the presentation and course of neuropsychiatric disorders at both ends of the life span.

Measuring cognitive reserve

Although the concept of cognitive reserve is intuitively appealing, it remains difficult to quantify experimentally. Early studies linking greater educational attainment, occupational complexity and current leisure activity to lower incident dementia [11,12] suggested that certain life achievements or experiences render individuals more capable of compensating for developing neuropathology. Two meta-analyses incorporating studies up to 2004 suggested that the risk of dementia is decreased by 46% in people with high cognitive reserve defined by these parameters [13,14]. Consequently questionnaires capturing these facets of life experience were developed as measures of cognitive reserve [15–18]. Such tools are useful as they provide a methodology for the uniform collection of pertinent variables across studies. However they are confounded because levels of education, occupation and leisure activity may render individuals more or less susceptible to dementia for other reasons. For example lower education is associated with lifestyles that lead to high blood pressure and type 2 diabetes which in turn increase the risk of cerebrovascular disease and thus

dementia [19••]. In addition, these measures do not help us understand if and how the putative neural processes underpinning cognitive reserve, outlined above, contribute to the variability in outcome in brain disorders.

Acknowledging this, a recent study devised a statistical approach to the measurement of cognitive reserve using the longitudinal cognitive data of over 300 elderly participants from diverse backgrounds [[19••]. Cognitive reserve was defined as 'the difference between an individual's expected cognitive performance, given a particular level of brain pathology, and their actual cognitive performance'. Latent variable modelling produced a baseline 'residual' measure (Mem-R) of episodic memory which was not attributable to individual differences in demographics or MRI brain volumes and accounted for ~50% of the variance in memory function. This measure also fulfilled the predictions of the cognitive reserve hypothesis: Mem-R correlated with premorbid IQ independently of the influence of education and in individuals with higher Mem-R there was a lower risk of converting to dementia and a weaker relationship between cognitive decline and an MRI index of neuropathology (brain atrophy). Importantly this finding has been replicated and extended in a different cohort [20]. These two studies therefore provide a promising unconfounded method for defining and measuring cognitive reserve which can be used in future to investigate the neural mechanisms underlying individual differences in outcome in various brain disorders.

Dementia

Despite the caveats over the use of proxy measures, advances in study design have provided support for the protective effect of cognitive reserve in dementia. Longitudinal cohort studies of middle-aged or elderly participants with normal or mildly impaired cognition can control for confounders and provide a powerful means of determining factors that predict the transition to dementia and how they interact. Additionally, the availability of known biological markers of dementia risk (decreased CSF abeta42, presence of an APOE e4 allele, reduced MRI hippocampal volume and increased uptake of the PET amyloid ligand Pittsburgh compound B) has enabled putative mechanisms of action of cognitive reserve to be explored.

Longitudinal studies have found that more years of education and higher premorbid IQ are associated with a later onset of dementia symptoms [21–23] and, following onset, cognitive decline is faster in those with these indices of higher cognitive reserve [22]. The latter phenomenon has been hypothesised to reflect increasing neuropathological load eventually overriding the protective effect of cognitive reserve. This has now been directly supported by a study showing that more years of education was related to lower CSF abeta42, an index of underlying brain pathology, both at the time of symptom onset and 2 years later [24].

Cross sectional studies of cortical amyloid binding provide support for the hypothesis that cognitive reserve delays the behavioural expression of Alzheimer neuropathology by finding that a proportion (19%) of cognitively normal elderly adults can have levels of brain amyloid binding as high as people with overt dementia and that years of education can modify the impact of cortical amyloid on the clinical diagnosis of Alzheimer's disease [25]. The relationship between cortical amyloid binding and cognitive function has also been shown to be weaker in people with greater education level and higher IQ [26].

Whether high cognitive reserve actually modifies Alzheimer's disease pathology before symptom onset has also been addressed but the evidence is equivocal. Higher premorbid IQ, education and occupation were found in one study to be associated with a slower rate of CSF abeta42 decline over 3 years in elderly cognitively normal people [27] but not in another study using similar measures of cognitive reserve over the same time course [23]. Studies examining the effect of life-long engagement with cognitively stimulating activities, rather than education and IQ, have also produced mixed results. One has found a correlation with hippocampal volume as assessed by serial MRI over 3 years: those with higher scores showing less hippocampal atrophy over time [28]. Greater participation in cognitively stimulating activities, especially in early and middle life, has also been associated with reduced cortical amyloid binding in a cross sectional study [29]. Although these support the view that cognitive stimulation can modify the Alzheimer pathological process this must be tempered by the finding of another study showing that mid/late life cognitive activity is not associated with either the degree of cortical amyloid deposition or future cognitive decline; better education and occupational attainment did ameliorate the effect of cortical amyloid on cognitive decline but again it did not modify the absolute level of cortical amyloid pathology [30••].

Longitudinal studies agree that indices of cognitive reserve do not modify the impact of the APOE e4 allele on increased risk of Alzheimer's disease [27,31,32] although one study found that cognitive reserve interacted to enhance the protective effect of the APOE e2 allele [32], an effect in a relative small number of participants that requires replication.

Overall, the existing results from longitudinal studies suggest that high cognitive reserve, albeit assessed by proxy measures, operates at the early stages of dementia by delaying the clinical expression of cognitive impairment. When these studies come to fruition with greater numbers it may be possible to answer the question